STEREOCHEMISTRY OF DISPLACEMENT REACTIONS OF ACETATE ION, CYANIDE ION, AND SUPEROXIDE ION SOLUBILIZED AS THEIR POTASSIUM SALTS WITH 18-CROWN-6 ETHER IN DIPOLAR AND NONPOLAR, APROTIC SOLVENTS

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

Neelam Kohli

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Chemistry

Georgia Institute of Technology

February, 1977

STEREOCHEMISTRY OF DISPLACEMENT REACTIONS OF ACETATE ION, CYANIDE ION, AND SUPEROXIDE ION SOLUBILIZED AS THEIR POTASSIUM SALTS WITH 18-CROWN-6 ETHER IN DIPOLAR AND NONPOLAR, APROTIC SOLVENTS

Approved:

Charles L. Liotta, Chairman

E. C. Ashby

Leon Zalkow

Date approved by Chairman MAR 10 1977

ACKNOWLEDGMENT

The author is grateful to her adviser, Dr. C. L. Liotta, for his patience, understanding, and timely advice throughout the progress of this thesis.

The author wishes to express her gratitude to Dr. E. C. Ashby and Dr. L. H. Zalkow for reading and critically evaluating this manuscript.

Finally, a special word of thanks goes to the author's husband, Taru, whose patience and persistant encouragement made this work possible.

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Anions, dissolved in dipolar and nonpolar, aprotic solvents as their potassium salts by means of 18-crown-6, have been shown to be powerful nucleophiles. These weakly solvated species have been termed "naked" anions. The stereochemistry of displacement reactions of "naked" acetate and "naked" cyanide with chiral α-phenethylchloride has been studied in acetonitrile, tetrahydrofuran, and benzene. "Naked" acetate undergoes nucleophilic displacement with inversion of configuration at the chiral center, whereas "naked" cyanide undergoes nucleophilic displacement with complete inversion of configuration. The reaction proceeded faster in acetonitrile as compared with benzene and tetrahydrofuran. The reaction of "naked" superoxide with chiral α-phenethylchloride in DMSO and C_6H_6 has been found to proceed with inversion of configuration.

CHAPTER I

HISTORICAL DISCUSSION

During the past few years, the concept of phase transfer reactions has been explored extensively by organic chemists. The pioneering work of Stark [1], Weber [2], and Markoza [3] on liquid-liquid phase transfer catalysis has proven to be synthetically very useful [4]. The extension into solid/liquid phase transfer reactions moderated by crown ethers, especially 18-crown-6 [8] by Liotta [5,6] and others [7], has extended the usefulness of this type of reaction.

In the classic work by Stark [1] on cyanide nucleophilicitics in the liquid/liquid phase transfer process, very good yields have been reported for the conversion of primary and secondary alkyl halides to alkyl cyanides. When activated halides (allylic and benzylic) were used, however, hydrolysis to the alcohol, not displacement by cyanide, was the principle product. The solid/liquid phase transfer method employing 18-crown-6 has been used to overcome this disadvantage. Nucleophilic displacements have been successfully carried out on substrates which react with nucleophilic solvents (H_2O, alcohols, or DMSO).

Since the time of their discovery, crown-ethers have been shown to have the ability to complex the metal cation of inorganic and organic salts [7,8,9] and to solubilize them in non-polar and dipolar aprotic solvents. The work of Sam and Simmons [7d] illustrated the solution of potassium permanganate in the presence of dicyclohexyl-18-crown-6 [10]

in solvents such as benzene where the permanganate anion acts as an efficient oxidizing agent. Sam and Simmons [1] have also observed [11] that potassium halides and potassium hydroxide in benzene possess strong nucleophilic properties. The observation of Liotta [8] on the reactivity of potassium fluoride [5] and potassium acetate [6] in non-polar solvents using 18-crown-6 ether has shown that these anions (termed "naked" anions) become extremely reactive in aprotic solution. Displacement reactions at 1°, 2°, 3°, and benzylic positions along with competing elimination process have been demonstrated with "naked acetate" as shown in Table 1 [6].

The data summarized in Table 1 deal specifically with the solvent acetonitrile. The same reactions carried out in benzene proceeded at a slower rate. In the absence of crown ether, little or no reaction took place under identical conditions covering the same periods of time. For instance, in the case of benzyl bromide, the most reactive substrate reported, less than 5% benzyl acetate was formed after several days with potassium acetate in the absence of crown ether whereas the conversion was complete within two hours in the presence of crown ether. Liotta et al. [12] have also observed that preliminary complexation of the salt with the crown ether is not necessary [9] and that a direct solution can be effected by this catalyst in aprotic solvents. This then allows the use of potassium halides in solvents not usually considered for such nucleophilic displacement reactions.

Studies by Liotta [13] and Durst [14] on substitution reactions by CN^{-} and nitrite ions in acetonitrile and methylene chloride, respectively, containing 18-crown-6 ether with large numbers of substrates have

Table 1. Reactions of "Naked" Acetate with Organic Substrates [6]

Substrate	Products	Concentrations (M) Crown	Concentrations (M) Substrate	Temp °C	Time (hrs)
Benzyl bromide	Benzyl acetate (100%)	0.16	3.4	25	2
n-$C_6H_{13}Br$	n-$C_6H_{13}OAC$ (100%)	0.10	1.4	25	150
n$C_8H_{17}Br$	n-$C_8H_{17}OAC$ (96%)	0.10	1.4	83	3
1,2-Dibromoethane	Ethylene diacetate(90%)	0.09	1.3	83	3
1,2-Dibromoethane	Ethylene diacetate(23%) 2-Bromoethyl acetate(77%)	0.06	1.9	83	3
2-Bromooctane	2-Acetoxyoctane(ca.90%) Octenes (ca. 10%)	0.10	1.4	83	20
2-Chloro-2-methyl-cyclohexanone	2-methylcyclohexenone(ca.10%) cis-2-acetoxy-6-methyl-cyclohexanone (ca. 54%) trans-2-acetoxy-6-methyl-cyclohexanone (ca. 10%) 2-acetoxy-2-methyl-cyclohexanone (ca. 25%)	0.15	2.9	83	1

been reported. Table 2 [13] illustrates reactions of "naked" cyanide with organic substrates in the presence of 18-crown-6.

The reactions were carried out by simply pouring a substrate-crown solution directly over excess, dry KCN, and stirring the two phase system vigorously at ambient or reflux temperatures until reaction was complete. Little or no reaction was found to take place in the absence of 18-crown-6 under the same conditions covering the same periods of time. In all cases 18-crown-6 was present in catalytic quantities, indicating that it behaved as a phase transfer catalyst. In general, reactions were more rapid in CH_3CN than in C_6H_6. The reaction of "naked" cyanide with benzyl chloride proceeded quickly and quantitatively to product under mild conditions (run 20, Table 2). With primary-substituted alkyl halides, the conversions to nitrile compounds were quantitative, with no elimination products detected (runs 1-12, Table 2). Displacement at secondary carbon produced primarily substitution products with only a small percentage of elimination products. These results compared favorably to those obtained with naked acetate [6] but are in direct contrast to those of "naked" fluoride [5], where large quantities of alkenes were obtained. It appears therefore that "naked" fluoride may be a stronger base than either "naked" cyanide or "naked" acetate.

Interestingly, it was found [13] that chlorides reacted much faster than corresponding bromides under the reaction conditions. For example, benzyl chloride reacted about 100 times faster than benzyl bromide (run 19, Table 2). This observation was contrary to the normally accepted leaving group order. It was also opposite to what had been observed with

Table 2. Reactions of "Naked" Cyanide with Organic Substrates in the Presence of 18-Crown-6

Substrate	Run	Solvent	Products (yield, %)	Concn, M		Temp, °C	t1/2, hr	t_{end}, hr
				Crown	Substrate			
1,3-Dibromopropane	1	CH_3CN	Glutaronitrile (97.3)	0.151	1.80	83	7	25
	2	CH_3CN	Glutaronitrile (94.9)	0.147	1.80	Ambient	10.5	48
	3	C_6H_6	Glutaronitrile (100)	0.147	1.80	90	12	40
	4	C_6H_6	Glutaronitrile (100)	0.147	1.80	Ambient	10	49
1,Bromo-3-chloropropane	5	CH_3CN	Glutaronitrile (100)	0.152	1.80	83	1.1	30
1,3-Dichloropropane	6	CH_3CN	Glutaronitrile (96.8)	0.154	1.80	83	0.23	1.5
1,4-Dibromobutane	7	CH_3CN	Adiponitrile (100)	0.141	1.80	83	6.5	14.5
	8	CH_3CN	Adiponitrile (100)	0.141	1.80	Ambient	11	57
1,4-Dichlorobutane	9	CH_3CN	Adiponitrile (94.7)	0.144	1.80	83	0.2	0.7
	10	CH_3CN	Adiponitrile (86)	0.144	1.80	Ambient	3	75
1,Bromohexane	11	CH_3CN	1-Cyanohexane (100)	0.138	1.80	83	10	40
1-Chlorohexane	12	CH_3CN	1-Cyanohexane (90.6)	0.139	1.80	83	0.5	2.2
2-Bromobutane	13	CH_3CN	2-Cyanobutane (69.7)	0.141	2.00	83	16	32
	14	C_6H_6	2-Cyanobutane (43.4)	0.140	2.01	90	58	66
2-Bromooctane	15	CH_3CN	2-Cyanooctane (56 (62) -octene (17)	0.119	2.00	83	14	78
2-Chlorooctane	16	CH_3CN	2-Cyanooctane (77.5) -octene (3.1)	0.122	2.00	83	59	244
Cyclohexyl bromide	17	CH_3CN	Cyclohexene (46)	0.132	1.80	83		53

Table 2. (Continued)

Substrate	Run	Solvent	Products (yield, %)	Concn, M		Temp, °C	t1/2, hr	t_{end}, hr
				Crown	Substrate			
Cyclohexyl chloride	18	CH_3CN	Cyclohexene (46)	0.146	1.80	83		122.5
Benzyl bromide	19	CH_3CN	Benzyl cyanide (100)	0.146	1.80	Ambient	13	25
Benzyl chloride	20	CH_3CN	Benzyl cyanide (94.2)	0.147	1.80	Ambient	0.08	0.4
	21	CH_3CN	Benzyl cyanide (20)	0.0	1.80	Ambient		75
α-Dichlorobenzene	22	CH_3CN	No reaction	0.145	1.80	83		109
Methacrylonitrile	23	CH_3CN	1,2-Dicyanopropane (91.9)	0.132	1.51	83	0.3	0.6
(Acetone cyanohydrin)					(1.78)			
	24	CH_3CN	1,2-Dicyanopropane (46)	0.132	1.52	Ambient		189
					(1.72)			
	25	CH_3CN	1,2-Dicyanopropane (77)	0.0	1.51	83	6.1	15
					(1.74)			

"naked" acetate [6] and "naked" fluoride [5]. With secondary halides, it appeared that bromides reacted more rapidly than chlorides, however, less alkene and a higher overall yield of substitution product were obtained with chloride.

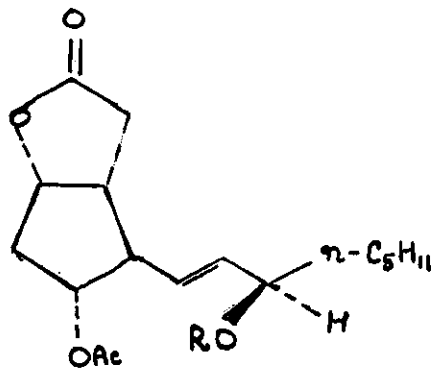
Recently, it has been observed that the solubility of KO_2 in dimethyl sulfoxide (DMSO) [15,16] can be increased considerably in the presence of stoichiometric amounts of "dicyclohexyl 18-crown-6" [10]. Corey [17] found that 18-crown-6 was a superior agent for dissolving KO_2 in organic solvents, allowing the preparation of highly reactive solutions of superoxide not only in DMSO but also in dimethylformamide (DMF), dimethoxyethane (DME), and even in diethyl ether.

In solution, potassium superoxide was found to be a reactive and effective oxygen nucleophile toward a variety of simple substrates [17,18]. The products of reaction under Corey's conditions were alcohols. The 15-R prostenoid structure (I) was converted to the 15-S-prostanoid system (III) by conversion of acetoxyalcohol (I) to reactive mesylate (II) by treatment with methanesulfonyl chloride and triethylamine which on subsequent treatment with KO_2 and 18-crown-6 in DMSO, DMF, and DME (1:1:1) and hydrolysis of acetate to hydroxy group gave the desired product (III) [17].

Table 3 illustrates the reactions of potassium superoxide with various organic halides and tosylates to produce the corresponding alcohols [18]. Substitution was the major reaction pathway with primary halides, however, substantial elimination occurs with secondary systems. Elimination was the predominant process observed from the reaction with

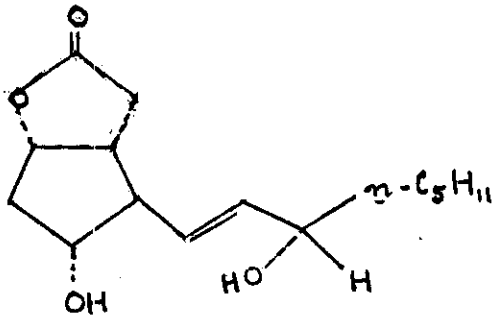
Table 3 . Reaction of Potassium Superoxide with Various Organic Halides and Tosylates

Substrate	Products(%)	Rel Reactivity
$1\text{-}C_8H_{17}I$	1-Octanol(46)	4.5
	1-Octene(3)	
	1-Octanal(11)	
$2\text{-}C_8H_{17}I$	2-Octanol(48)	3.3
	Octenes(48)	
	2-Octanone(<1)	
$1\text{-}C_8H_{17}Br$	1-Octanol(63)	1.0
	1-Octene(<1)	
	1-Octanal(12)	
$2\text{-}C_8H_{17}Br$	2-Octanol(51)	0.98
	Octenes(34)	
	2-Octanone(<1)	
$CH_3(CH_2)_2C\text{-}(CH_3)_2Br$	2-Methyl-2-pentanol(20)	0.90
	2-Methylpentenes(30)	
$1\text{-}C_8H_{17}Cl$	1-Octanol(34)	0.089
	1-Octene(~1)	
	1-Octanal(5)	
$2\text{-}C_8H_{17}Cl$	2-Octanol(36)	0.020
	Octenes(12)	
	2-Octanone(<1)	
$1\text{-}C_8H_{17}OTs$	1-Octanol(75)	
	1-Octene(<1)	1.0
	1-Octanal(1)	
$2\text{-}C_8H_{17}OTs$	2-Octanol(75)	
	Octenes(23)	
	2-Octanone(<1)	
$C_6H_5CH_2Cl$	Benzyl alcohol(41)	
	Benzaldehyde(6)	2.9



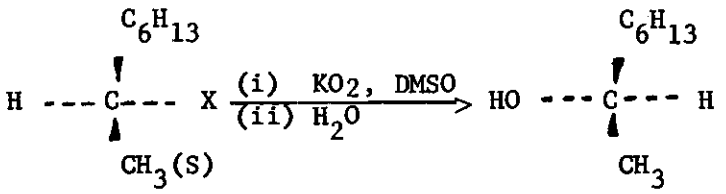
(I, R = H

II, R = SO_2CH_3)



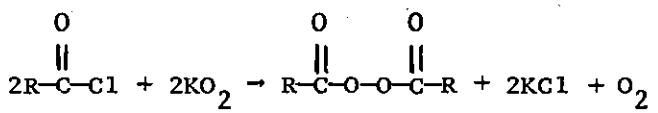
(III)

tertiary halide 2-bromo-2-methylpentane. These facts parallel similar observations involving the reactions of other basic nucleophiles with alkyl halides [5,13,16]. Optimum alcohol yields were obtained at superoxide to alkyl halide molar ratios of ≧ 3. The observed substrate reactivity was shown to be of following order: benzyl > primary > secondary > tertiary > aryl and I > Br > Cl. San Filippo and Romano showed that carbon-oxygen bond formation took place with inversion of configuration at chiral centre [18]. Reaction of the tosylate of (+) - (S) -2-octanol (α_{589}^{20} + 7.97°, optical purity 99.4%) with potassium superoxide produced (-) - (R)-2-octanol (α_{589}^{20} - 7.71°) corresponding to an optical purity and overall stereoselectivity of 97%. Similar reaction with (-) - (R) - 2-bromooctane [19] afforded (+) - (S)-2-octanol in 90% optical purity (95% net inversion)



(1)

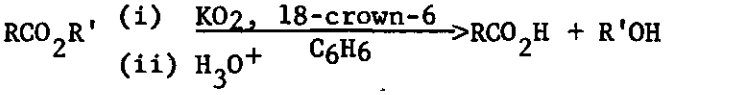
Diakyl peroxides were obtained by using equal molar amount of potassium superoxide and alkyl substrate [21]. Recently synthesis of diacyl peroxides have been reported by reaction of KO_2 with acyl halides [20]



(2)

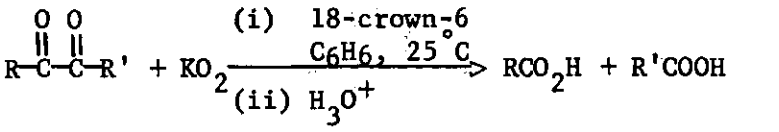
In contrast to the conditions used for dialkyl peroxides synthesis [21] the above reaction proceeded readily without the use of a crown-ether, even when benzene was used as reaction medium.

The reaction of carboxylic esters with potassium superoxide in benzene in the presence of 18-crown-6 ether produced, upon aqueous work up, the corresponding carboxylic acid and alcohol in good to excellent yields [22].

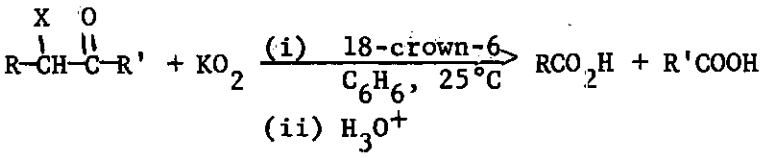


(3)

The reaction of α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids with potassium superoxide in benzene in the presence of 18-crown-6 ether resulted in oxidative cleavage of these compounds to carboxylic acids.



(4)



(5)

R' = OH, OR, alkyl, aryl, X = OH, Cl, Br

CHAPTER II

EXPERIMENTAL

Reagents and Instrumentation

Acetonitrile

A.C.S. certified acetonitrile was obtained from Fisher Scientific Company, Atlanta, Georgia and was used without further purification.

Tetrahydrofuran

A.C.S. certified tetrahydrofuran was obtained from Fisher Scientific Company and was used without further purification.

Benzene

A.C.S. certified benzene was obtained from Fisher Scientific Company and was used without further purification.

Potassium Salts

A.C.S. certified potassium acetate and potassium bromide were obtained from Fisher Scientific Company. The salts were dried in the oven at 120°C for a minimum of 12 hours.

Potassium Cyanide

Fisher certified A.C.S. reagent grade potassium cyanide used in this study was vacuum (0.3 mm Hg) dried for a minimum of 24 hours.

Potassium Superoxide

Obtained from Organic/Inorganic Chemical Corporation was finely ground in a glove bag under an atmosphere of dry nitrogen. All weighings of potassium superoxide were carried out in a dry-box.

Nuclear Magnetic Resonance Spectrometer

All NMR's were obtained using a varian A-60 spectrometer.

Infra-red Spectrophotometer

A Beckman IR-12 spectrophotometer was used for all infra-red work.

Melting Point Apparatus

A mel-temp unit was used to obtain all melting points in degrees centigrade using an uncalibrated thermometer.

Weighing Balance

A 5-place mettler H20T balance was used for accurate weighings. A mettler type H-15 and a Mettler K-7 macro balance were used for all other weighings.

Polarimeter

Optical rotations of neat liquid compounds were determined in 1 dm capillary cell using Bellingham and Stanley Ltd. (No. 397619) polarimeter. Optical rotations in solution were determined using a Bendix Ericsson automatic polarimeter. Path length of the polarimeter cells used were determined using standard sucrose solution.

Experimentation

1. Preparation of 1,4,7,10,13,16-Hexaoxacyclooctadecane (18-Crown-6) [8b]

A 3000 ml 3-necked flask equipped with mechanical stirrer, reflux condenser, and addition funnel was charged with triethylene glycol (113 g, 0.78 mol) and tetrahydrofuran (600 ml). Stirring was started and 60% KOH solution (109 g dissolved in 120 ml of water) was added. The solution became warm and after 15 minutes of stirring (solution darkened) a solution of 3,6-dioxa-1,8-dichloroctane (140 g, 0.75 mol) in 100 ml tetrahydrofuran was added in a stream. After the above solution was completely added, the flask was heated at reflux and stirred vigorously for 19 hours. The solution turned reddish brown. It was then allowed to cool and the major portion of the THF and H_2O was evaporated under reduced pressure (first at 30°C to evaporate the THF and then at 60°C to evaporate as much water as possible). The resulting slurry was diluted with 500 ml of dichloromethane. The solid material was removed by filtration and was washed with additional dichloromethane to remove any adsorbed crown ether. The organic solutions were combined and dried over $MgSO_4$ overnight. The dried solution was then filtered and the CH_2Cl_2 removed under reduced pressure. The residue was distilled at 0.5-0.6 mm pressure and the following fractions were collected: I: 60°C - 120°C, II: 123°C - 124°C, III: 145°C - 150°C, IV: 150°C - 180°C. Crude crown was then purified in the following manner: 50 g of crude 18-crown-6 (Fraction 3) was transferred into a 250 ml erlenmeyer flask equipped with a magnetic stirring bar and a calcium sulphate drying tube, 125 ml of acetonitrile was added and the resulting slurry was heated on a hot plate to effect solution. The solution was stirred vigorously and allowed to cool. Fine white crystals of crown-acetonitrile complex were deposited and the flask

was cooled in a dry-ice acetone bath. The crown-acetonitrile complex precipitated out and was collected by filtration. The complex was stored overnight under nitrogen. The hygroscopic crystals of crown-acetonitrile were transferred into a 500 ml round-bottom flask equipped with a magnetic stirring bar and vacuum take off. Acetonitrile was taken off at low pressure (0.1 - 0.5 mm) with gentle heating over 8-9 hours leaving 25 g (50% yield) of the pure colorless crown.

M.P. 38-39°C (Lit. [8a] 39-40°C). NMR (60 MHz, CCl_4) 3.56 PPM (singlet). Mass spectrum M and M + 1 at m/e 264 and 265 and other fragments at m/e 89, 87, 59, 45, 44, 43, and 31.

2. Preparation of 3,5 Dinitrobenzoate of α-Phenethyl Alcohol [24]

Twenty-four ml of dry pyridine was added to a mixture of 7.7 g (0.063 mol) of α-phenethyl alcohol (Eastman) and 14.7 g (0.064 mol) of 3,5 dinitrobenzoyl chloride (Eastman) in a 250 ml erlenmeyer flask. The resulting solution was heated over steam bath for 10-15 minutes. The reaction mixture was poured into a mixture of 50 ml of distilled water and 20 ml of 5% sodium-carbonate solution (in order to induce solution of any 3,5 dinitrobenzoic acid). The solution was extracted with 50 ml of ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent taken off under reduced pressure. The crude 3,5 dinitrobenzoate obtained was recrystallized twice from anhydrous ethanol. Yield = 9.4 g (48%) M.P. = 98°C (Lit. [25] 99-100°C).

3. Preparation of α-Phenethyl Acetate [26]

A 50 ml round bottom flask equipped with reflux condenser, a Drierite drying tube and a magnetic stirrer was charged with 10 g

(0.08 mol) of α-phenethyl alcohol and 10 g (0.097 mol) of acetic anhydride. The reaction mixture was refluxed for 20 minutes, cooled, and distilled under reduced pressure to give 11 g (82%) of α-phenethyl acetate, bp 73-75°C (2.5 Torr) (Lit. [27] 97°C (12 Torr)).

4. Reaction of 3,5 Dinitrobenzoate of α-Phenethyl Alcohol with Potassium Acetate and 18-Crown-6 Ethers ("Naked" Acetate) in Tetrahydrofuran

A dry 25 ml 3-necked round bottom flask equipped with a teflon-coated stirring bar, a reflux condenser, a gas outlet tube, and a thermometer was charged with 0.137 g (0.0005 mol) of 18-crown-6 ether, 1 g (0.01 mol) of dry potassium acetate and 6 ml of tetrahydrofuran. The mixture was stirred for 30 minutes and then 1.58 g (0.005 mol) of 3,5-dinitrobenzoate of α-phenethyl alcohol (obtained from II) was added and the reaction mixture refluxed under nitrogen. The extent of reaction was followed by glc. Less than 10% of the reaction took place even after stirring for 48 hours. The above reaction was repeated with equivalent amount of 18-crown-6 ether, keeping all other conditions identical. Less than 10% of reaction took place in 48 hours. Under identical conditions, reactions were carried out in acetonitrile and similar results were obtained.

5. Reaction of α-Phenethyl Chloride with Potassium Acetate and 18-Crown-6 Ether (One Tenth Mole Percent) in Acetonitrile

Following the same procedure as outlined in (4), 7 g (0.05 mol) of α-phenethyl chloride (Eastman) was added to a vigorously stirred mixture of dry powdered potassium acetate (9.8 g, 0.1 mol) and 18-crown-6

ether (1.32 g, 0.005 mol) in 50 ml dry acetonitrile. The mixture was stirred at 45°C for 27 hours, cooled, treated with 30 ml of water and extracted twice with 40 ml of ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. Fractionation of crude product gave 7 g (86%) of α-phenethyl acetate bp 73 - 75°C (2.5 Torr) (Lit. [27] 97°C (12 Torr)).

6. Reaction of α-Phenethyl Chloride with Potassium Acetate and 18-Crown-6 Ether (Equivalent Amount) in Acetonitrile

The above reaction was repeated keeping all other conditions identical and using an equivalent amount of crown ether. The reaction was complete in 20 hours and produced α-phenethyl acetate in 85% isolated yield. bp 73 - 75°C (2.5 Torr) (Lit. [27] 97°C (12 Torr)).

7. Reaction of α-Phenethyl Chloride with Dry Potassium Cyanide and 18-Crown-6 Ether (One Tenth Mole Percent) in Acetonitrile

The above reaction was repeated using the same procedure as outlined in (5), α-phenethyl cyanide was obtained in 79% isolated yield, bp 70 - 72°C (1.5 Torr) (Lit. [28] 74 - 78°C (1 Torr)). The reaction mixture in this case was stirred at 50°C for 50 hours.

8. Reaction of α-Phenethyl Chloride with Dry Potassium Cyanide and 18-Crown-6 Ether (Equivalent Amount) in Acetonitrile

α-Phenethyl cyanide was obtained (78% isolated yield) by following the same procedure as in (7) except an equivalent amount of 18-crown-6 ether was used and the mixture was allowed to react for 22 hours.

9. Reaction of α-Phenethyl Chloride with Dry Potassium Bromide and 18-Crown-6 Ether

Following the same procedure as in (4), α-phenethyl chloride

(1 g, 0.007 mol) was added to a vigorously stirred mixture of dry potassium bromide (1.67 g, 0.014 mol) and 18-crown-6 ether (1.32 g, 0.007 mol) in 6 ml of acetonitrile. The reaction mixture was stirred at 50°C. The reaction was followed by glc. After 20 hours, equilibrium was reached and mixture of α-phenethyl chloride and bromide in 63% and 37% (glc yield), respectively were obtained. Fifty mg of α-phenethyl bromide was collected by glc and NMR, IR, and Mass Spectrum of the product were identical to that of an authentic sample of α-phenethyl bromide (K and K Chemical Company).

10. Optical Resolution of α-Phenethyl Alcohol

(i) Preparation of hydrogen-phthalate salt of α-phenethyl alcohol.

Racemic α-phenethyl alcohol (122.17 g, 1 mol) and 148.0 g (1.00 mol) phthalic anhydride and 118.50 g (1.50 mol) of pyridine were heated at 65°C for 3 hours in a 1000 ml round bottom flask equipped with reflux condensor [29,30]. Following Pickard and Kenyon's procedure [31], the mixture was cooled and poured into 100 ml of 5% sodium carbonate solution. The resulting mixture was allowed to sit for 6-8 hours to hydrolyze any anhydride starting material. The alkaline solution was then extracted three times with 100 ml of ether to remove unesterified alcohol. The acid ester product precipitated as an oil by dilute hydrochloric acid. The oil was then extracted with chloroform. Phthalic acid being insoluble in dry chloroform was thus readily removed. The chloroform layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The 221.0 g (82% yield) of crude phthalate obtained was recrystallized from benzene M.P. = 108°C (Lit. [31] 108°C).

(ii) Formation of brucine hydrogen phthalate salt of α-phenethyl alcohol. Following Downer and Kenyon's [32] method, 73.00 g (0.185 mol) of brucine was dissolved in a warm solution of 50 g (0.185 mol) of racemic hydrogen phthalate of α-phenethyl alcohol in 170 ml acetone and was left to crystallize for three days. The crystalline material (50 g, M.P. 136°C, decomposition) which separated was recrystallized four times from minimum amount of hot methylacetate. The 30 g (M.P. 154°C, decomposition) of brucine salt was obtained in the form of fine needles and 7.0 g were obtained from methyl acetate mother liquors. Following Eliel's method [33], this salt (37.0 g) was dissolved in methanol and poured into 20 ml of dilute hydrochloric acid and the oily phthalate was extracted with ether. The ether layer was washed with water, dried over anhydrous sodium-sulfate and filtered. The solvent was removed under reduced pressure and the hydrogen phthalate (15.0 g) obtained was dissolved in 30 ml of cold carbon disulphide. It was allowed to sit for 24 hours and was then decanted from hard crystals of hydrogen phthalate. The supernatant liquid was warmed and diluted with 15 ml of petroleum ether, and (-) - (S) - α-phenethyl hydrogen phthalate (11.5 g) separated as clusters of fine needles. The ester was hydrolyzed with 5.0 N sodium hydroxide solution and 5.1 g of (-) - (S) - α-phenethyl alcohol was isolated by extractive steam distillation with ether. $[\alpha]_D^{25} = -41.6^\circ$ ($\ell = 1$, neat, 95.4% optical purity).

After approximately one week, the acetone mother-liquor from which the main portion of brucine salt had been removed, deposited a crop of fine needles which were recrystallized three times from acetone. Hydrogen

phthalate salt (35 g) was obtained in the same way as described above which on recrystallization from carbon disulphide and extractive steam distillation with ether gave 5.3 g of (+) - (R) - α-phenethyl alcohol. $[\alpha]_D^{25} = 40.5^\circ$ ($\ell = 1$, neat, 92.8% optical purity). Maximum rotation of optically active α-phenethyl alcohol taken as $[\alpha]_D^{25} = 43.6^\circ$ [31].

The combined yield of optically active alcohols was 45%.

11. a Preparation of (-) - (S) - α-Phenethyl Chloride from (-) - (S) - α-Phenethyl Alcohol and Thionyl Chloride

Following the procedure of McKenzie and Clough [34], 5.9 g of thionyl chloride was added slowly to 2 g (0.016 mol) of (-) - (S) - α-phenethyl alcohol (K and K Chemical Co.) $[\alpha]_D^{25} = -43.26^\circ$ ($\ell = 1$, neat, 99.5% optical purity) in 10 ml of chloroform at 25°C. The reaction mixture was stirred for 15 minutes after the addition of thionyl chloride was completed and then thionyl chloride and chloroform were taken off at low pressure. Subsequent distillation furnished 1.9 g (85% yield) of (-) - (S) - α-phenethyl chloride. $[\alpha]_D^{25} = -43.49^\circ$ ($\ell = 1$, neat, 36.8% optical purity). b.p. 76-77°C (17 mm) (Lit. [27] b.p. 78-79°C (15 Torr), 37% net retention).

11. b Preparation of (+) - (R) - α-Phenethyl Chloride from (+) - (R) - α-Phenethyl Alcohol and Thionyl Chloride [34]

Following the procedure of McKenzie and Clough [34], 6 g of thionyl chloride was added slowly to 2.5 g (0.02 mol) of (+) - (R) - α-phenethyl alcohol (K and K Chemical Co.) $[\alpha]_D^{25} = +40.09^\circ$ ($\ell = 1$, neat, 92.3% optical purity) in 10 ml of chloroform. After the addition of thionyl chloride was completed, thionyl chloride and chloroform were taken off at low pressure at room temperature. Subsequent fractional distillation

gave 2.5 g (87% yield) of (+) - (R) - phenethyl chloride. $[\alpha]_D^{25}$ = + 40.72° (ℓ = 1, neat, 34.5% optical purity), b.p. 76-77°C (17 Torr) (Lit. [27] b.p. 78-79°C (15 Torr)), with 37% retention of configuration.

12. Preparation of (+) - (R) - α-Phenethyl Chloride from (-) - (S) - α-Phenethyl Alcohol and Phosphorus Oxychloride [36]

A 250 ml 3-necked round bottom flask equipped with an addition funnel, a sintered glass tube, a gas outlet tube, and a teflon coated magnetic stirring bar was charged with 80 ml of pyridine. Hydrogen chloride gas was passed through pyridine. The resulting solution was cooled to -10°C - 15°C in an ice-salt bath and 20 g (0.16 mol) of (-) - (S) - α-phenethyl alcohol $[\alpha]_D^{25}$ = - 43.26° (ℓ = 1, neat, 99.5% optical purity) in 200 ml of chloroform in one portion and 22 ml (0.25 mol) of phosphorous oxychloride were added slowly dropwise. The reaction mixture was allowed to warm to room temperature for 18-19 hours, decomposed with ice, and extracted with chloroform. The chloroform layer was extracted with 85% phosphoric acid, washed three times with water, dried over $MgSO_4$, filtered and distilled to give 17 g (74% yield) (+) - (R) - α-phenethyl chloride, b.p. 76-77°C (17 Torr) (Lit. [27] b.p. 78-79°C (15 Torr)) $[\alpha]_D^{25}$ = + 86.24° (ℓ = 1, neat, 73.1% optical purity) with 73.5% inversion. [Maximum rotation of α-phenethyl chloride taken as α_D = 125.4° [35]].

13. Preparation of (+) - (R) - α-Phenethyl Acetate from (+) - (R) - α-Phenethyl Alcohol and Acetic Anhydride [26]

(+) - (R) - α-phenethyl alcohol (5.09 g, 0.04 mol) $[\alpha]_D^{25}$ = + 40.09° (ℓ = 1, neat, 92.3% optical purity) and 6.50 g (0.044 mol) of acetic

anhydride were refluxed for 15 minutes in 25 ml round-bottomed flask equipped with reflux condenser and drying tube. The reaction mixture was cooled and fractionally distilled at low pressure to give 6.00 g (89% yield) of (+) - (R) - α-phenethyl acetate b.p. 73°C (2.5 Torr), (Lit. [27] 97°C (12 Torr)). $[\alpha]_D^{25} = +112.06°$ ($\ell = 1$, neat, 88.9% optical purity). Therefore, the reaction proceeded with 96% retention of configuration.

14 . Optical Resolution of Hydratropic Acid

(i) Preparation of (-) - (S) - hydratropic acid from (-) - (S) - phenyl-ethylamine salt [38]. Racemic hydratropic acid (61.94 g, 0.42 mol) and 50.00 g of (-) - (S) - phenethylamine were dissolved in a hot mixture of 800 ml of benzene and 200 ml of absolute ethanol and the phenethylamine salt was allowed to crystallize. The crystals were filtered, washed with cold benzene, dried and weighed (see Table 4). The salt (0.4 g) was set apart and the acid was liberated with dilute sulfuric acid, extracted with ether and isolated by evaporation of the solvent. The acid was dissolved in ethanol and optical activity determined. The principal part of the salt was recrystallized from a mixture of benzene and ethanol (4:1) four times and each time 0.4 g was set apart and acid liberated with dilute sulfuric acid and optical rotation determined as shown in Table 4. The (-) - (S) - phenethylamine salt of (-) - (S) - hydratropic acid was obtained as colorless needles. The progress of the resolution was as shown in Table 4.

Table 4. Progress of Resolution of (-) - (S)-Phenethylamine Salt of (-) - (S)-Hydratropic Acid

Crystallization No.	ml of Solvent	g of (-) Acid Salt	$[\alpha]_D^{25}$	
1	1000	36 g	-56°	[ℓ=0.211,C,2.06,EtOH]
2	300	20 g	-60°	[ℓ=0.211,C,2.04,EtOH]
3	160	15 g	-72°	[ℓ=0.211,C,2.08,EtOH]
4	130	10 g	-74.97°	[ℓ=0.211,C,2.08,EtOH]

(ii) (-) - (S) - Hydratropic acid. The 10 g of (-) - (S) - phenethylamine salt was decomposed with diluted sulfuric acid and the liberated acid was extracted with ether and solvent removed. The residue was distilled to give 3.8 g of (-) acid, b.p. 146°C (10 Torr) (Lit. [39] b.p. 148°C (12 Torr)) $[\alpha]_D^{23}$ = -99.11° (ℓ = 1, neat) $[\alpha]_D^{25}$ = -74.97° (ℓ = 0.211, C, 2.08, ethanol). 94.8% optical purity. [Maximum rotation reported [41] is $[\alpha]_D^{25}$ = 79.0°].

15. Preparation of (-) - (S) - Hydratropamide from (-) - (S) - Hydratropic Acid [38]

A 25 ml round-bottomed flask equipped with reflux condenser and drierite drying tube was charged with 3.8 g (0.025 mol) of (-) - (S) - hydratropic acid $[\alpha]_D^{25}$ = -74.97° (ℓ = 0.211, C, 2.08, ethanol). Contents of flask were refluxed for 20 min with 3.8 g (0.032 mol) thionyl chloride till evolution of HCl gas ceased. Excess thionyl chloride was removed at low pressure and the acid chloride obtained was dissolved in benzene and 8 ml of concentrated ammonia was added. The benzene layer

was washed twice with water and the solvent removed at low pressure. The residue was recrystallized from a mixture of petroleum ether and benzene (1:1) and 2.5 g (65% overall yield from hydratropic acid) of amide crystallized as glistening leaves. M.P. 100.5°C (Lit. [38] 101.5-102°C).

16. Optically Active (-) - (S) - α-Phenethyl Cyanide from Optically Active Amide and Thionyl Chloride

Following the procedure of Rickborm and Jensen [40], a 10 ml round-bottomed flask equipped with a reflux condenser 2.5 g (0.016 mol) of amide and 2.5 g (0.021 mol) of thionyl chloride were stirred for 30 minutes at room temperature and then refluxed for another 30 minutes. Excess thionyl chloride was removed under reduced pressure and the distilled at 70-73°C (1.5 Torr) (Lit. [28] 74-78°C (1 Torr)). The infrared and NMR spectrum were identical to the authentic sample of α-phenethyl cyanide (Eastman) (-) - (S) - phenethyl cyanide $[\alpha]_D^{25} = +15.35^\circ$ (ℓ = 0.211, C, 3.21, CH_3CN). Assuming that no racemization takes place in all the transformations carried out, 94.8% optically pure hydratropic acid to acid chloride to amide and finally to cyanide, extrapolation to 100% optical purity $[\alpha]_D^{25} = +16.19^\circ$ (ℓ = 0.211, C, 3.21, CH_3CN).

17. a Reaction of (+) - (R) - α-Phenethyl Chloride with "Naked" Acetate in Acetonitrile

Following the same procedure as in (4), 2.00 g (0.014 mol) of (+) - (R) - α-phenethyl chloride $[\alpha]_D^{25} = +71.07^\circ$ (ℓ = 1, neat, 60.2% optical purity) was added to a previously stirred mixture of dry powdered potassium acetate (3 g, 0.03 mol) and 18-crown-6 ether (3.8 g, 0.014 mol) in 50 ml dry acetonitrile. After 20 hours of stirring at 45° the reaction

mixture was cooled and treated with 15 ml of water and extracted with 40 ml of ether. The ether extract was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The 2.0 g (85% yield) of (-) - (S) - α-phenethyl acetate $[\alpha]_D^{25} = -69.6^\circ$ ($\ell = 1$, neat, 55.2% optical purity) distilled at 73°C (2 Torr) (Lit. [27] 97°C (12 Torr)) (with 91% net inversion).

17. .b Optical Stability Control Run

Following exactly the same procedure as in (a), 1.5 g (0.007 mol) of (-) - (S) - α-phenethyl acetate $[\alpha]_D^{25} = -77.32^\circ$ ($\ell = 1$, neat, 61.3% optical purity), was added to a mixture of dry powdered potassium acetate (1.9 g, 0.019 mol) and 18-crown-6 ether (2.4 g, 0.004 mol) in 30 ml of dry acetonitrile and stirred at 45°C for 20 hours. The reaction work up gave 1.43 g (95%) of (-) - (S) - α-phenethyl acetate b.p. 73-74°C (2 Torr). (Lit. [27] 97°C (12 Torr)) $[\alpha]_D^{25} = -73.79^\circ$ ($\ell = 1$, neat, 58.5% optical purity). Extent of racemization was $\frac{61.3\% - 58.5\%}{61.3\%} \times 100 = 4.5\%$

18. a Reaction of (+) - (R) - α-Phenethyl Chloride with "Naked" Acetate in Tetrahydrofuran

Following the same procedure as in 17 (a), 1.5 g (0.010 mol) of (+) - (R) - α-phenethyl chloride $[\alpha]_D^{25} = +71.07^\circ$ ($\ell = 1$, neat, 60.2% optical purity) was added to a vigorously stirred mixture of dry powdered potassium acetate (2 g, 0.020 mol) and 18-crown-6 ether (2.64 g, 0.010 mol) in dry THF (10 ml). The mixture was stirred at 55°C for 170 hours. Only 70% of reaction had gone to completion. The reaction was worked up and the solvent was taken off at reduced pressure. The glc analysis of it indicated the presence of α-phenethyl chloride (33%) and α-phenethyl

acetate (67%). The rotation of mixture was $[\alpha]_D^{25}$ = (-) 26.25° (ℓ = 1, neat).

If the reaction had gone to completion with 100% inversion $[\alpha]_D^{25}$ should be = -75.9° (ℓ = 1, neat) (which is rotation of (-) - (S) - phenethyl acetate 60.2% optical purity.) The rotation of authentic mixture of 67% (-) - (S) - α-phenethyl acetate and 33% (+) - (R) - α-phenethyl chloride would be (-) 75.9° x 0.67 - (+) 71.07° x 0.33 = -27.39° whereas the observed rotation is $[\alpha]_D^{25}$ = (-) 26.25° which is in close agreement to above calculated rotation. [Note: The density of α-phenethyl chloride at 25°C is d_4^{25} = 1.0621 (calculated from McKenzie and Clough's [42] data d_4^{20} = 1.0632 and $dt^4/dt \cong -0.0003°/°C$. The density of α-phenethyl acetate at 25°C is 1.0151 [37]. For calculation of specific rotation of the mixture, the densities of two are assumed to be close. Density of α-phenethyl acetate is used for the calculation of specific rotation of mixture.]

18. b Optical Stability Control Run

Following the same procedure as in 18 (a), 2 g (0.012 mol) of (+) - (R) - α-phenethyl acetate $[\alpha]_D^{25}$ = +112.06° (ℓ = 1, neat, 88.9% optical purity) was added to a previously stirred mixture of dry powdered potassium acetate (2.4 g, 0.02 mol) and 18-crown-6 ether (3.2 g, 0.012 mol) in 15 ml dry THF. The mixture was stirred at 55°C for 170 hours. The reaction work up gave 1.9 g (95% yield of (+) - (R) - α-phenethyl acetate b.p. 73°C (2 Torr) (Lit. [27] 97°C (12 Torr)) $[\alpha]_D^{25}$ = +110.34° (ℓ = 1, neat, 87.5% optical purity). Extent of racemization = $\frac{88.9\% - 87.5\%}{88.9\%} \times 100 = 1.6\%$.

19. a Reaction of (+) - (R) - α-Phenethyl Chloride with "Naked" Acetate Anion in Benzene

Following the same procedure as in 17 (a), 1.5 g (0.01 mol) of (+) - (R) - α-phenethyl chloride, $[\alpha]_D^{25} = +71.07^\circ$ ($\ell = 1$, neat, 60.2% optical purity) was added to previously stirred mixture of dry powdered potassium acetate (2 g, 0.02 mol) and 18-crown-6 ether (2.64 g, 0.01 mol) in dry 10 ml of benzene. The mixture was stirred at 55°C for 170 hours. Only 36% of the reaction had gone to completion. The reaction mixture was worked up and the solvent was taken off at reduced pressure. The glc analysis of it indicated the presence of α-phenethyl chloride (65%) and α-phenethyl acetate (35%). The rotation of the mixture was $[\alpha]_D^{25} = +21.00^\circ$ ($\ell = 1$, neat). Had the reaction gone to 100% completion (with 100% inversion) $[\alpha]_D^{25}$ should have been -75.9° ($\ell = 1$, neat) (which is the rotation of (-) - (S) - α-phenethyl acetate, 60.2% optical purity). For an authentic mixture of 35% (-) - (S) - α-phenethyl acetate and 65% (+) - (R) - α-phenethyl chloride, the calculated rotation would be $+71.07 \times 0.65 - 75.9 \times 0.35 = (+) 19.62^\circ$. The observed rotation in our case, however, is $+21^\circ$ which is in close agreement with the above calculated rotation. [Note: The density of α-phenethyl chloride was used for calculation of the specific rotation of the mixture.]

19. b Optical Stability Control Run

Following the same procedure as in 17 (a), 2 g (0.012 mol) of (+) - (R) - α-phenethyl acetate $[\alpha]_D^{25} = +112.06^\circ$ ($\ell = 1$, neat, 88.9% optical purity) was added to a previously stirred mixture of dry powdered potassium acetate (2.4 g, 0.02 mol) and 18-crown-6 ether (3.2 g, 0.012

mol) in dry benzene (15 ml). The mixture was stirred at 55°C for 170 hours. Working up the reaction mixture gave 1.9 g (95% yield) (+) - (R) - α-phenethyl acetate b.p. 73-74°C (2 Torr) (Lit. [27] 97°C (12 Torr) $[\alpha]_D^{25} = +111.3^\circ$ ($\ell = 1$, neat, 88.26% optical purity). Extent of racemization = $\frac{88.9\% - 88.26\%}{88.9\%} \times 100 = 0.7\%$.

20. a Reaction of (+) - (R) - α-Phenethyl Chloride with "Naked" Cyanide in Acetonitrile

Following the same procedure as in 17 (a), 1.5 g (0.01 mol) of (+) - (R) - α-phenethyl chloride $[\alpha]_D^{25} = +75.6^\circ$ ($\ell = 1$, neat, 64.03% optical purity) was added to a mixture of dry powdered potassium cyanide (1.4 g, 0.02 mol) and 18-crown-6 ether (2.64 g, 0.01 mol) in dry CH_3CN (10 ml). The mixture was stirred at 50°C for 22 hours. The reaction work up gave α-phenethyl cyanide 1.1 g (84%) b.p. 73°C (1.5 Torr) (Lit. [28] 74-78°C (1 Torr) $[\alpha]_D^{25} = 0$ ($\ell = 0.211$, C, 3.2, CH_3CN).

20. b Optical Stability Control Run

Following the same procedure as in 20 (a), 0.320 g (0.0024 mol) (+) - (S) - α-phenethyl cyanide $[\alpha]_D^{25} = +15.35^\circ$ ($\ell = 0.211$, C, 3.2, CH_3CN) was added to a mixture of dry powdered potassium cyanide (0.32 g, 0.0049 mol) and 18-crown-6 ether (0.644 g, 0.0025 mol) in dry CH_3CN (10 ml). The mixture was stirred at 50°C for 22 hours. The reaction work up gave 0.298 g (93% yield) α-phenethyl cyanide b.p. 74-76°C (1.5 Torr) (Lit. [28] 74-78°C (1 Torr)). $[\alpha]_D^{25} = 0$ ($\ell = 0.211$, C, 3.2; CH_3CN).

21. a Reaction of (+) - (R) - α-Phenethyl Chloride with "Naked" Cyanide in Tetrahydrofuran

Following the same procedure as in 17 (a), 1.5 g (0.01 mol)

(+) - (R) - α-phenethyl chloride $[\alpha]_D^{25} = +71.07^\circ$ ($\ell = 1$, neat, 60.2% optical purity) was added to a mixture of dry powdered potassium cyanide (1.3 g, 0.02 mol) and 18-crown-6 ether (2.64 g, 0.01 mol) in dry tetrahydrofuran (10 ml). The mixture was stirred at 55°C for 175 hours. Only 75% of the reaction had gone to completion. The reaction mixture was worked up and the solvent was taken off at reduced pressure. The glc analysis of it indicated the presence of (+) - (R) - α-phenethyl chloride (30%) and α-phenethyl cyanide (70%). The rotation of mixture was $[\alpha]_D^{25} = +20.00^\circ$ ($\ell = 1$, neat).

The calculated rotation of authentic mixture of 30% (+) - (R) - α-phenethyl chloride 60.2% optical purity and 70% racemic α-phenethyl cyanide would be $[\alpha]_D^{25} = +21.32^\circ$. [Note: The density of α-phenethyl chloride was used to calculate the specific rotation of mixture.]

21. b Optical Stability Control Run

Following exactly the same procedure as used in 20 (b) gave α-phenethyl cyanide (93% yield) $[\alpha]_D^{25} = 0$ ($\ell = 0.211$, C, 3.2, CH_3CN) b.p. 74-75°C (1.5 Torr) (Lit. [28] 74-78°C (1 Torr)).

22. a Reaction of (+) - (R) - α-Phenethyl Chloride with "Naked" Cyanide in Benzene

Following the same procedure as in 17 (a), 1.5 g (0.01 mol) (+) - (R) - α-phenethyl chloride $[\alpha]_D^{25} = +71.07^\circ$ ($\ell = 1$, neat, 60.2% optical purity) was added to previously stirred mixture of dry powdered potassium cyanide (1.3 g, 0.02 mol) and 18-crown-6 ether (2.64 g, 0.01 mol) in dry benzene (10 ml). The mixture was stirred at 55°C for 173 hours. Only 38% of the reaction had gone to completion. The glc analysis

of the worked up reaction mixture indicated the presence of (+) - (R) - α-phenethyl chloride (64%) and α-phenethyl cyanide (36%). The rotation of mixture was $[\alpha]_D^{25} = +45.9^\circ$ ($\ell = 1$, neat). The calculated rotation of mixture of 64% (+) - (R) - α-phenethyl chloride (60.2% optical purity) and 36% racemic α-phenethyl cyanide would be $[\alpha]_D^{25} = +45.48^\circ$ whereas observed value is $[\alpha]_D^{25} = +45.9^\circ$.

22. b Optical Stability Control Run

Following exactly the same procedure as used in 20 (b) gave α-phenethyl cyanide (96% yield). $[\alpha]_D^{25} = 0$ ($\ell = 0.211$, C, 3.2, CH_3CN) b.p. 74-75°C (1.5 Torr) (Lit. [28] 74-78°C (1 Torr).

23. a Reaction of (-) - (S) - α-Phenethyl Chloride with Potassium Superoxide and 18-Crown-6 Ether in DMSO

Following San Filippo's [18] procedure, a 100 ml 3-necked flask equipped with addition funnel, gas outlet tube, a rubber septum, and a teflon coated stirring bar was charged with 2.84 g (0.04 mol) of powdered potassium superoxide and 1.056 g (0.004 mol) 18-crown-6 ether. The flask was covered immediately with 60 ml of dry dimethyl sulfoxide. To this vigorously stirred mixture was added (-) - (S) - α-chloroethyl benzene (1.5 g, 0.01 mol) $[\alpha]_D^{25} = -73.8^\circ$ ($\ell = 1$, neat, 62.5% optical purity) at 25°C. The resulting mixture was allowed to stir for 75 minutes and then cautiously treated with 30 ml of water saturated with NaCl and finally extracted with three 50 ml portions of petroleum ether. Stripped off petroleum ether and dried over $MgSO_4$. The glc analysis of crude reaction mixture gave acetophenone (6-7%) and alcohol (40%). (+) - (R) -α-Phenethyl alcohol $[\alpha]_D^{25} = +31.79^\circ$ ($\ell = 0.290$, C, 1.968, $CHCl_3$)

(57.2% optical purity) was isolated in 33% yield, b.p. 93°C (14 Torr). (Lit. [27] 102-103°C (20 Torr)) (with 91.6% net inversion).

23. b Optical Stability Control Run

Following the same procedure as in 23 (a) 3.4 g (0.048 mol) of dry powdered potassium superoxide and 1.27 g (0.0048 mol) of 18-crown-6 ether in a vigorously stirred mixture with dry DMSO (60 ml) was added (-) - (R) - α-phenethyl alcohol (1.5 g, 0.012 mol) $[\alpha]_D^{26}$ = (+) 48.67° (ℓ = 0.211, C, 2.08, $CHCl_3$)(92.9% optical purity). The mixture was stirred at 25°C for 75 minutes. The reaction mixture was worked up in the same way as in XXIII (A) and gave 0.75 g (50%) of (+) - (R) - α-phenethyl alcohol b.p. 93°C (14 Torr) (Lit. [27] 102-103°C (12 Torr)) $[\alpha]_D^{26}$ = +46.2° (ℓ = 0.211, C, 2.054, $CHCl_3$)(88.2% optical purity). Extent of racemization = $\frac{92.9\% - 88.2\%}{92.9\%} \times 100 = 5\%$.

24. a Reaction of (-) - (S) - α-Phenethyl Chloride with Potassium Superoxide and 18-Crown-6 Ether in Benzene

Following the same procedure as in 23 . (a), to a vigorously stirred mixture of dry powdered potassium superoxide (7.1 g, 0.1 mol) and 18-crown-6 ether (6.6 g, 0.025 mol) in dry benzene (120 ml) was added (-) - (S) - α-phenethyl chloride (3.5 g, 0.025 mol) $[\alpha]_D^{26}$ = -74.4° (ℓ = 1, neat, 59.3% optical purity). The mixture was stirred at 25°C for 3.5 hours. The glc analysis of crude mixture showed the composition to be alcohol (41%) and acetophenone (7%). Working up reaction mixture gave 1.03 g (34%) of (+) - (R) - α-phenethyl alcohol b.p. 93-94°C (14 Torr) (Lit. [27] 102-103°C (20 Torr)) $[\alpha]_D^{26}$ = +28.53° (ℓ = 0.211, C, 2.00, $CHCl_3$)(54.5% optical purity) (93% net inversion).

24. b Optical Stability Control Run

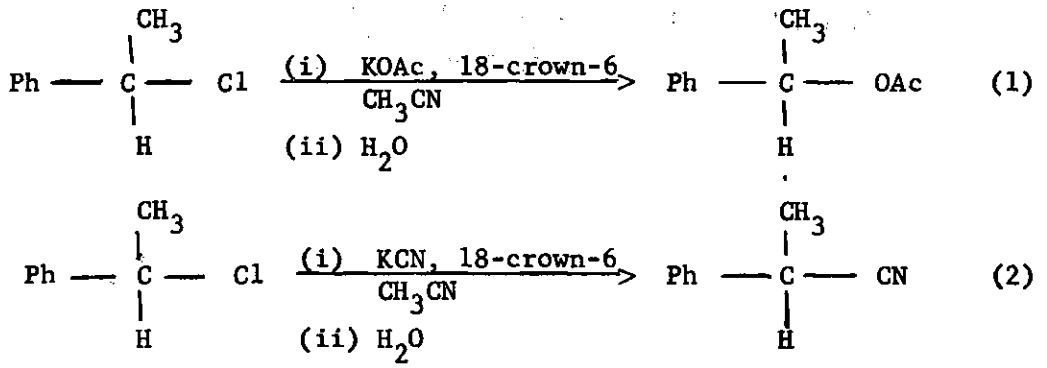
Following the same procedure as in 23 (a), to a mixture of dry powdered potassium superoxide (3.4 g, 0.048 mol) and 18-crown-6 ether (1.27 g, 0.0048 mol) in dry benzene (60 ml), was added (+) - (R) - α-phenethyl alcohol (1.5 g, 0.012 mol) $[\alpha]_D^{26} = +48.67^\circ$ (ℓ = 0.211, C, 2.08, $CHCl_3$) (92.9% optical purity). The mixture was stirred at 25°C for 3.5 hours. Working up the reaction mixture gave 0.73 g (50% yield) of (+) - (R) - α-phenethyl alcohol b.p. 92-93°C (14 Torr) (Lit. [27] 102-103°C (20 Torr)) $[\alpha]_D^{26} = +48.07^\circ$ (ℓ = 0.211, C, 2.14, $CHCl_3$) (91.8% optical purity). Extent of racemization = $\frac{92.9\% - 91.8\%}{92.9\%} = 1\%$.

CHAPTER III

RESULTS AND DISCUSSION

The study reported herein was performed to determine the stereochemical course in the reaction of "naked" acetate and "naked" cyanide in acetonitrile, benzene, and tetrahydrofuran, and "naked" superoxide in DMSO and C_6H_6 with optically active α-phenethylchloride.

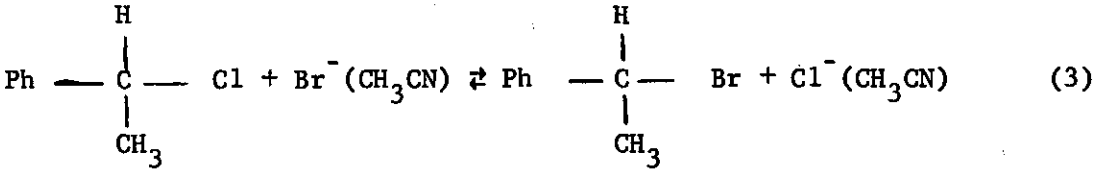
The reactions of "naked" acetate and "naked" cyanide were first run with racemic α-phenethylchloride in the presence of one-tenth molar and equimolar amounts of 18-crown-6.



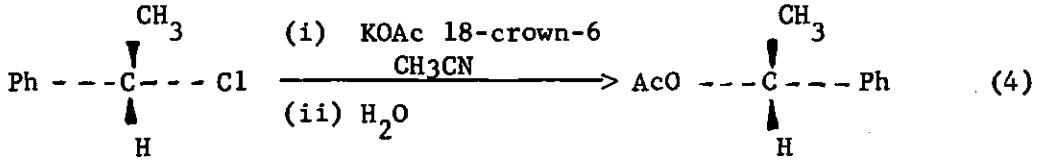
The reaction proceeded faster with equivalent amounts of crown ether. The expected acetate or cyanide product was obtained in each case. In the absence of crown ether less than 10% of the reaction took place under the same conditions and during the same period of time. In contrast to the crown rate catalyzed reactions is the work reported by Steigman and Hammet [27]. Several weeks of reaction time were necessary to prepare (-) (S) - α-phenethylacetate from (+) - (R) - α-phenethylchloride

$[\alpha_{5461} = +13.7]^{\circ}$ and anhydrous potassium acetate in dry acetone.

Reaction of "naked" bromide with α-phenethylchloride at equilibrium gave a mixture of 63% chloride and 37% bromide. This result may be simply understood in terms of bond energies. The C—Cl bond is stronger than C—Br bond thus shifting the equilibrium toward the left. This simple analysis ignores solvation of the anion species. This is, however, considered to contribute little to the overall position of equilibrium (Equation 3).



(3)



(4)

(R) (S)

Table 5 shows that the reaction of (+) - (R) - α-phenethylchloride $[\alpha]_D^{25} = +71.07^{\circ}$ [$\ell = 1$, neat, 60.2% optical purity] with potassium acetate in the presence of an equivalent amount of 18-crown-6 ether in acetonitrile gave (-) - (S) - α-phenethyl acetate, $[\alpha]_D^{25} = -69.6^{\circ}$ [$\ell = 1$, neat, 55.2% optical purity] with 92% net inversion of configuration. This indicates that carbon-oxygen bond formation involves backside displacement (S_N2) at the chiral centre (Equation 4). An optical stability experiment was also carried out with (-) - (S) - α-phenethyl acetate under exactly identical conditions. Reaction of (-) - (S) - α-phenethyl acetate with "naked" acetate $[\alpha]_D^{25} = -77.32^{\circ}$ [1 = 1, neat, 61.3% optical purity] gave

Table 5. Reactions of Optically Active Substrates with Potassium Acetate, Potassium Cyanide and Potassium Superoxide

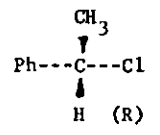
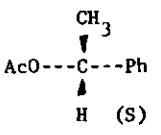
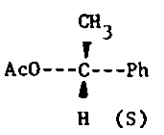
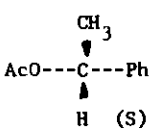
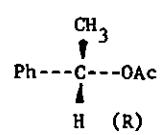
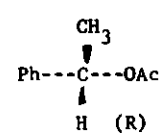
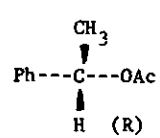
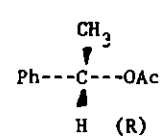
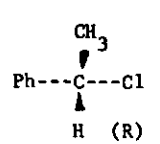
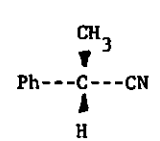
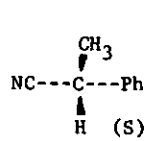
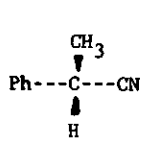
Run	Mx	Solvent	Substrate	Rotation $[\alpha]_D$	Optical Purity of Substrate %	Product	Rotation $[\alpha]_D$	Optical Purity of Product %	Net Steric Course %	Temp C	Time hr	Isolated Yield %	GC Yield %
1	KOAc	CH_3CN		$[\alpha]_D^{25}$= + 71.07 [l = 1, neat]	60.2		$[\alpha]_D^{25}$= -69.6 [l = 1, neat]	55.2	92 (Inv)	45	20	85	93
2	KOAc	CH_3CN		$[\alpha]_D^{25}$= - 77.32 [l = 1, neat]	61.3		$[\alpha]_D^{25}$= - 73.79 [l = 1, neat]	58.5	4.5 (Rac)	45	20	95	100
3	KOAc	THF		$[\alpha]_D^{25}$= + 112.06 [l = 1, neat]	88.9		$[\alpha]_D^{25}$= + 110.34 [l = 1, neat]	87.5	1.6 (Rac)	55	170	95	98
4	KOAc	C_6H_6		$[\alpha]_D^{25}$= + 112.06 [l = 1, neat]	88.9		$[\alpha]_D^{25}$= + 111.3 [l = 1, neat]	88.2	0.7 (Rac)	55	170	95	98
5	KCN	CH_3CN		$[\alpha]_D^{25}$= + 75.06 [l = 1, neat]	64.03		$[\alpha]_D^{25}$= 0 [l = 0.211, C,3.20, CH_3CN]	0	100 (Rac)	50	22	84	91
6	KCN	CH_3CN		$[\alpha]_D^{25}$= + 75.6 [l= 0.211, C,3.21, CH_3CN	95		$[\alpha]_D^{25}$= 0 [l = 0.211, C,3.20, CH_3CN	0	100 (Rac)	50	22	93	99

Table 5. (Continued)

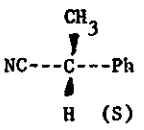
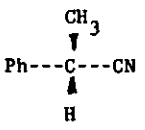
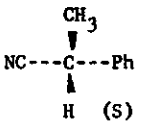
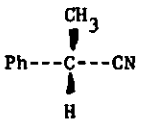
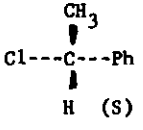
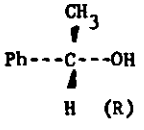
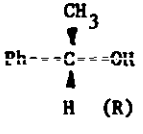
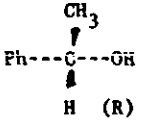
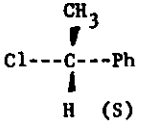
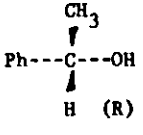
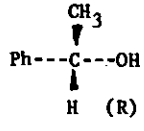
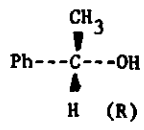
Run	Mx	Solvent	Substrate	Rotation $[\alpha]_D$	Optical Purity of Substrate %	Product	Rotation $[\alpha]_D$	Optical Purity of Product %	Net Steric Course %	Temp C	Time hr	Isolated Yield %	GC Yield %
7	KCN	THF		$[\alpha]_D^{25}$ = + 15.35 [1 = 0.211, C, 3.21, CH_3CN]	95		$[\alpha]_D^{25}$ = 0 [1 = 0.211, C,3.20,CH_3CN]	0	100 (Rac)	55	175	93	99
8	KCN	C_6H_6		$[\alpha]_D^{25}$ = + 15.35 [1 = 0.211, C,3.21, CH_3CN]	95		$[\alpha]_D^{25}$ = 0 [1 = 0.211, C,3.21, CH_3CN]	0	100 (Rac)	55	173	96	100
9	KO_2	DMSO		$[\alpha]_D^{25}$ = - 73.8 [1 = 1, neat]	62.5		$[\alpha]_D^{25}$ = + 31.79 [1 = 0.290, C,1.96, $CHCl_3$]	0	91.6 (Inv)	25	1.25	33	40
10	KO_2	DMSO		$[\alpha]_D^{26}$ = + 48.67 [1 = 0.211, C,2.00, $CHCl_3$]	92.9		$[\alpha]_D^{26}$ = + 46.2 [1 = 0.211, C,2.00, $CHCl_3$]	88.2	5 (Rac)	26	1.25	50	56
11	KO_2	C_6H_6		$[\alpha]_D^{26}$ = - 74.4 [1 = 1, neat]	59.3		$[\alpha]_D^{26}$ = + 28.53 [1 = 0.211, C,2.00, $CHCl_3$]	54.5	92.9 (Inv)	26	3.5	34	41
12	KO_2	C_6H_6		$[\alpha]_D^{26}$ = + 48.67 [1 = 0.211, C,2.00, $CHCl_3$]	92.9		$[\alpha]_D^{26}$ = 48.07 [1 = 0.211, C,2.01, $CHCl_3$]	91.8	1 (Rac)	26	3.5	50	54

Table 5. (Continued)

a. Equivalent amount of 18-crown-6 was used in all the runs except for runs 9 and 10 (in which one-third mole percent was used).

b. Max. Rotation of optically active α-Phenethyl chloride taken as $\alpha_D = 125.4$[35]

c. Max. Rotation of optically active α-Phenethyl acetate $[\alpha]_D = 126.1$[37]

d. Max. Rotation of (+) - (S) - α-Phenethyl cyanide was taken as $[\alpha]_D^{25} = 16.16$ [l = 0.211, C, 3.21, CH_3CN].

e. Max. Rotation of (+) - (R) - α-Phenethyl alcohol in $CHCl_3$ as $[\alpha]_D^{26} = +52.39$ [l = 0.211, C, 2.00, $CHCl_3$].

f. N.M.R., I·R, and Mass spectrum of products were identical to the authentic sampler.

g. Rotation of (+) - (R) - α-Phenethyl alcohol in $CHCl_3$ $[\alpha]_D^{25} = +55.76$ [l = 0.290, C,1.96, $CHCl_3$].

acetate $[\alpha]_D^{25} = -73.79^\circ$ [$\ell = 1$, neat, 58.5% optical purity], the extent of racemization under these reaction conditions being equal to 61.3 - 58.5/61.3 x 100 = 4.5%. The reaction of "naked" acetate in the solvents THF and benzene was much slower than in acetonitrile. In acetonitrile the reaction was complete within 20 hours whereas in THF only 70% reaction had taken place in 170 hours and in benzene only 36% in 170 hours. Optical stability experiments were also carried out in THF and benzene. These experiments demonstrated that the extent of racemization of the acetate product was only 1.6% and 0.7%, respectively, as compared to 4.5% in acetonitrile.

The results in Table 6 are consistent with the data reported by San Filippo et al. [19].

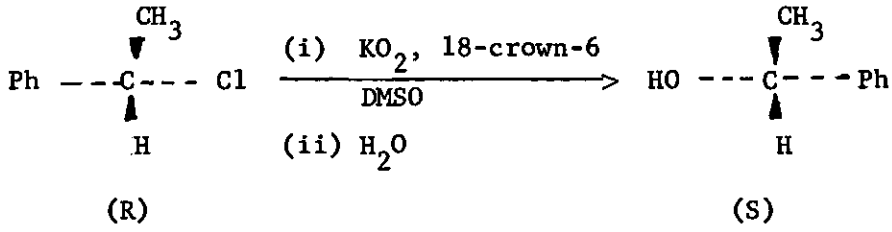
The reaction of "naked" cyanide with optically active α-phenethyl-chloride proceeded with racemization in acetonitrile, benzene, and tetrahydrofuran. Optical stability experiments run with optically active α-phenethyl cyanide (made by an alternate procedure) showed that racemization of the product occurred under these reaction conditions (Table 5).

The reaction of potassium superoxide with (-) - (S) - α-phenethyl-chloride in DMSO gave (+) - (R) - α-phenethyl alcohol with net 92% inversion in 33% isolated yield (Equation 5). An interesting comparison is the work done by San Filippo and L. H. Romano [18] who found that the reaction of the tosylate of (+) - (S) - 2-octanol [$\alpha_{589}^{20} + 7.97^\circ$, optical purity 99.4%] with potassium superoxide produced (-) - (R) - 2-octanol ($\alpha_{589}^{20} - 7.71^\circ$) corresponding to an optical purity and overall selectivity of 97%. Similar reaction with (-) - (R) - 2-bromooctane [19] afforded

Table 6. Reaction of (+) - (S) - 2-Octyl Tosylate with Potassium Fluoride, Lithium Chloride, Potassium Bromide, and Lithium Iodide

MX (concn, M)	Solvent	Temp, (Torr)	Reaction time, hr	2-Halooctane (%)	α^{20}_{589}	Optical purity, %	C-X bond refraction, cm^3, 20° (λ = 589)	Octene, (%)
KF (5.0)	Triethylene glycol	110 (4.0)	3	2-Fluorooctane (52)	- 9.99	~100	1.44	27
LiCl (5.0)	Triethylene glycol	110 (4.0)	2	2-Chlorooctane (80)	-30.72	97.2	6.74	16
KBr (1.2)	Triethylene glycol	65 (0.1)	2	2-Bromooctane (75)	-41.56	95.4	9.80	8.0
LiI (1.2)	Tetraethylene glycol	90 (0.1)	1.5	2-Iodooctane (83)	-19.32	30.6	14.08	8.0

(+) - (S) -octanol in 90% optical purity (95% net inversion)



(5)

The reaction of potassium superoxide in benzene with (-) - (S) - α-phenethylchloride $[\alpha]_D^{26} = -74.4^\circ$ [$\ell = 1$, neat, 59.3% optical purity] also gave (+) - (R) - α-phenethyl alcohol $[\alpha]_D^{26} = +28.53^\circ$ [$\ell = 0.211$, C, 2.00, $CHCl_3$, 54.5% optical purity] with 93% inversion in 34% isolated yield. (Table 5). Optically active α-phenethyl alcohol was also allowed to react with potassium superoxide in benzene and DMSO under identical reaction conditions to study the racemization of product. In DMSO (+) - (R) - α-phenethyl alcohol was 5% racemized whereas in benzene there was only 1% racemization. An interesting fact was that about 35-40% of alcohol product disappeared when allowed to react with potassium superoxide in benzene for about 3.5 hours. Only 7-8% of ketone product was identified.

$$R_2CHOH + KO_2 \rightarrow R_2CHOK + HO_2 \qquad (6)$$

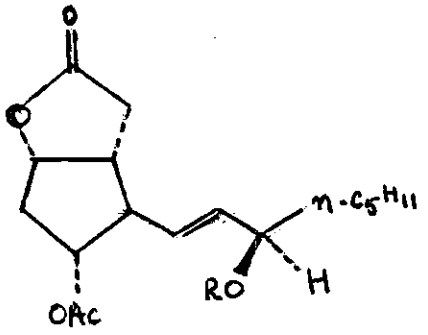
$$HO_2 \rightarrow 0.5\ H_2O_2 + 0.5\ O_2 \qquad (7)$$

$$R_2CHOK + HO_2 + O_2 \rightarrow R_2CO + KOOH \qquad (8)$$

The reaction of both "naked" acetate and superoxide anion in displacement

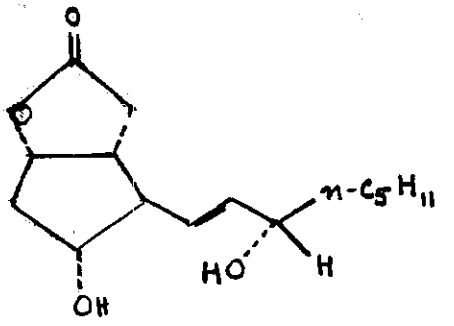
reactions represent the incorporation of an oxygen functionality at a carbon center. It is interesting to compare the results of "naked" acetate and superoxide anion as far as stereochemistry and yields are concerned. The acetate was obtained in 85% isolated yield whereas the alcohol was obtained in 33-34% yield. Since elimination can be an important pathway in reactions with potassium superoxide, in certain cases use of the above observation could be useful.

The replacement of the hydroxy group in a stereospecific manner in steroids generally requires a number of steps. Corey [17] has made use of potassium superoxide to convert 15-R-peosternoid structure (I) to 15-s-prostanoid (III) system through mesylate (II).



(I, R = H

II, R = SO_2CH_3)



(III)

Instead reaction with potassium acetate in crown ether could be used to form the acetate with inversion of configuration which could be cleaved with potassium superoxide to give alcohol in required

stereochemistry in good to excellent yields [22].

CHAPTER IV

CONCLUSION

The reactions of both "naked" acetate and "naked" superoxide with optically active α-phenethylchloride represent incorporation of oxygen functionality with inverstion of configuration at the chiral center. The reactions of "naked" acetate with optically active chloride produces the acetate in much better yields but longer reaction periods are required as compared to that of superoxide anion. Reactions of "naked" cyanide with the above substrate proceeded with racemization (because of racemization of final cyanide product).

REFERENCES

1. (a) C. M. Starks, J. Amer. Chem. Soc., 93, 191 (1970); (b) C. M. Starks and R. M. Owens, J. Amer. Chem. Soc., 95, 3613 (1973); (c) C. M. Starks, First Fall Organic Conference, Cape Cod, Mass., Oct. 1, 1973.

2. (a) W. P. Weber, K. V. Scherer, D. T. Sepp, Tetrahedron Lett., 2983 (1974); (b) W. P. Weber and J. P. Shepherd, Tetrahedron Lett., 4907 (1972); (c) W. P. Weber, G. W. Gokel, and I. K. Ugi, Angew. Chem. internat. Ed., 11, 520 (1972).

3. (a) M. Makosza and M. Wawrzyniewicz, Tetrahedron Lett., 4659 (1969); (b) M. Makosza, A. Jonczyk, B. Serafin, Tetrahedron Lett., 1351 (1971).

4. (a) E. V. Dehmlow, Angew. Chem. internat. Ed., 13, 170 (1974); (b) J. Dockx, Synthesis, 441 (1973).

5. C. L. Liotta and H. P. Harris, J. Amer. Chem. Soc., 96, 2252 (1974).

6. C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, Tetrahedron Lett., 2417 (1974).

7. (a) H. D. Durst, Tetrahedron Lett., 2421 (1974); (b) H. D. Durst, J. W. Zubrick, and J. R. Kieczykowski, Tetrahedron Lett., 1777 (1974); (c) D. J. Sam and H. E. Simmons, J. Amer. Chem. Soc., 96, 2252 (1974); (d) D. J. Sam and H. E. Simmons, J. Amer. Chem. Soc., 94, 4024 (1972); (e) D. J. Cram, Science, 183, 801 (1974); (f) C. J. Pederson and H. K. Frensdorff, Angew. Chem. internat. Ed., 11, 16 (1972); (g) J. J. Christensen, J. O. Hill, and R. M. Izatt, Science, 174, 459 (1971); (h) C. J. Pederson, J. Amer. Chem. Soc., 89, 7017 (1967), 92, 391 (1970).

8. Pederson's Nomenclature. 18-Crown-6 is 1,4,7,10,13,16-hexaoxacyclooctadecane and can be synthesized according to the procedure of (a) R. N. Green, Tetrahedron Lett., 1793 (1972) or by that of (b) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, J. Org. Chem., 39, 2445 (1974). This material is supplied commercially by P.C.R., Inc., P. O. Box 1466, Gainesville, Florida, 32602.

9. (a) C. J. Peterson, J. Amer. Chem. Soc., 89, 7017 (1967); (b) ibid., 92, 391 (1970), Fed. Proc. Fed. Amer. Soc. Exp. Biol., 27, 1305 (1968).

10. Peterson's Nomenclature. Dicyclohexyl-18-crown-6 is 2,3,11,12-dicyclohexyl-1,4,7,10,13,16-hexaoxacyclooctadecane. This material is available from Aldrich Chemical Co., Milwaukee, Wis., 53233.

11. D. J. Sam and H. E. Simmons, First Fall Organic Conference, Cape Cod, Mass., Oct. 1, 1973, Abstract #11.

12. C. L. Liotta and H. P. Harris, First Fall Organic Conference, Cape Cod, Mass., Oct. 1, 1973, Abstract #5.

13. F. L. Cook, C. W. Bowers, and C. L. Liotta, J. Org. Chem., 39, 3416 (1974).

14. J. W. Zubrick, Betty I. Dunbar, Dupont Durst, Tetrahedron Letts., I, 71 (1975).

15. E. L. Johnson, K. H. Pool, and R. E. Hamm, Anal. Chem., 38, 183 (1966).

16. A. U. Khan, Science, 168, 476 (1970).

17. E. J. Corey, K. C. Nicolaon, Mascukatsu Shibasaki, Yoshimasa Machida, and Christopher S. Shriner, Tetrahedron Letts., 37, 3183 (1975).

18. Joseph San Filippo, Jr., Chueng-Ing Chern, Joan S. Valentine, J. Org. Chem., 40, 1678 (1975).

19. J. San Filippo and L. S. Romano, J. Org. Chem., 40, 1514 (1975).

20. Roy A. Johnson, Tetrahedron Letts., 5, 331 (1976).

21. R. A. Johnson and E. G. Nidy, J. Org. Chem., 40, 1680 (1975).

22. J. San Filippo, Jr., L. J. Romano, Chueng-Ing Chern, and Joan S. Valentine, J. Org. Chem., 41, 486 (1975).

23. J. San Filippo, Jr., Chueng-Ing Chern, J. S. Valentine, J. Org. Chem., 41, 1077 (1976).

24. William A. Bonner and Clair J. Collins, J. Amer. Chem. Soc., 75, 4516 (1953).

25. W. Reppe, O. Schlichiting, K. Klager, and T. Toepel, Liebigs Ann. Chem., 48, 560 (1948).

26. P. A. Levene and R. E. Marker, J. Biol. Chem., 97, 379 (1932).

27. J. Steigman and L. P. Hammett, J. Amer. Chem. Soc., 59, 2536 (1937).

28. O. H. Oldenziel and A. M. Van Lensen, Tetrahedron Letts., 16, 1357 (1973).

29. A. J. Houssa and J. Kenyon, J. Chem. Soc., 2260 (1930).

30. Hyp. J. Dauben, Jr., and Laybon L. McCoy, J. Amer. Chem. Soc., 81, 5404 (1959).

31. R.H.Pickard and J. Kenyon, J. Chem. Soc., 99, 45 (1911).

32. E. Downer and J. Kenyon, J. Chem. Soc., 1156 (1939).

33. E. Eliel, J. Amer. Chem. Soc., 71, 3970 (1949).

34. A. McKenzie and G. W. Clough, J. Chem. Soc., 103, 694 (1913).

35. R. L. Burwell, Jr., A. D. Shields, and H. Hart, J. Amer. Chem. Soc., 76, 908 (1954).

36. A. Streitwieser, Jr., L. Reif, J. Amer. Chem. Soc., 86, 1993 (1964).

37. Kurt Mislow and Joseph Brenner, J. Amer. Chem. Soc., 75, 2318 (1953).

38. K. Petterson, Ark. Kemi, 10, 283 (1956).

39. R. Roger and D. G. Neilson, J. Chem. Soc., 627 (1960).

40. B. Rickborn and R. Jensen, J. Org. Chem., 27, 4608 (1962).

41. A. Fredga, Arkiv. Kemi, 7, 241 (1954).

42. A. McKenzie and G. W. Clough, J. Chem. Soc., 103, 687 (1913).